Data Quality and Transparency in the ToxCast Program

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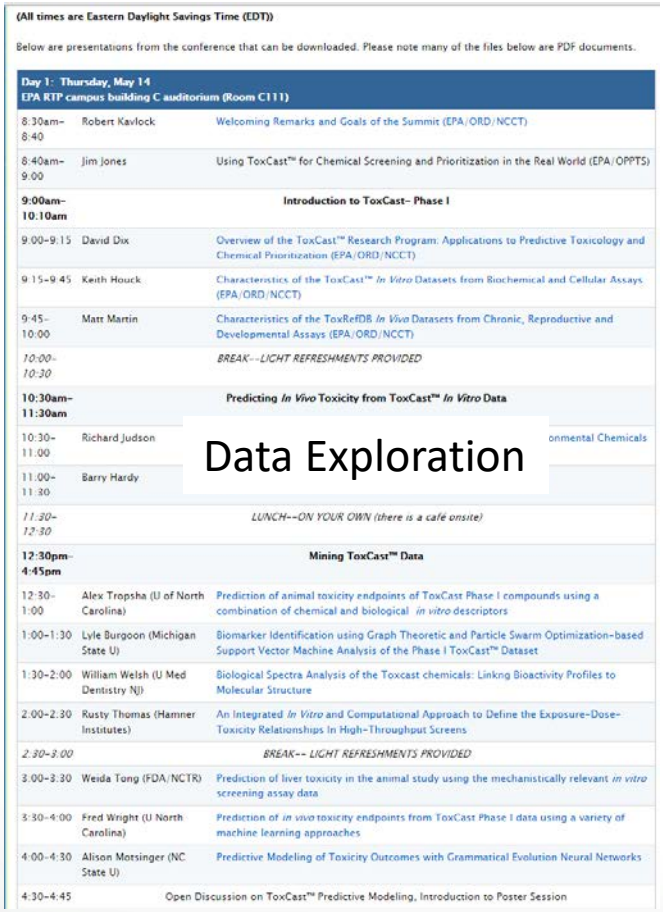
Evolution of the ToxCast Program

1st ToxCast Data Summit (2009)



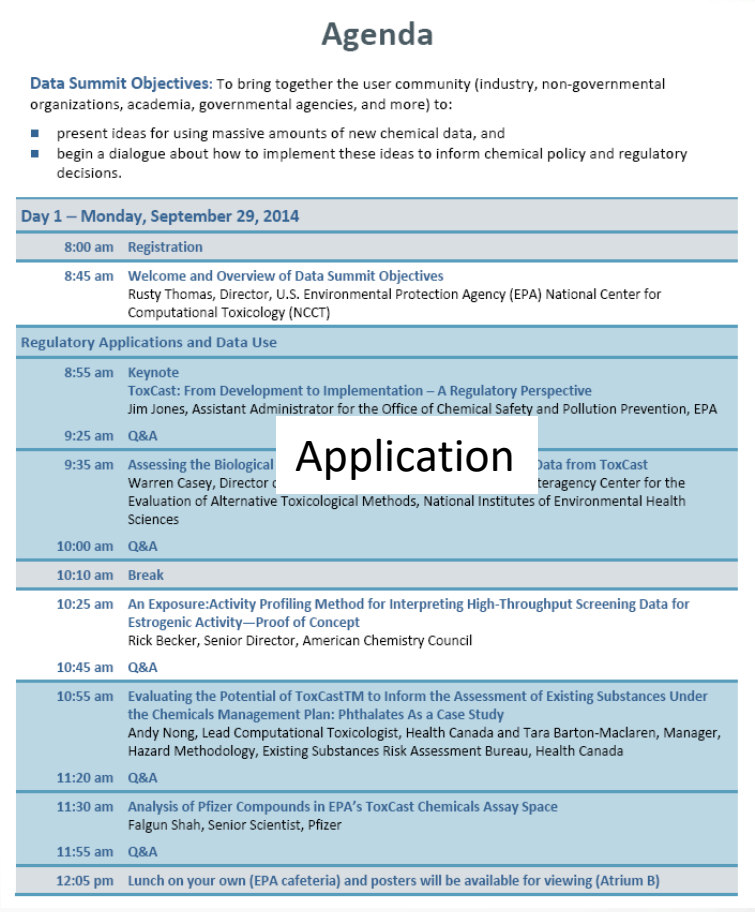
(All times are Eastern Daylight Savings Time (EDT))

Below are presentations from the conference that can be downloaded. Please note many of the files below are PDF documents.

Day 1: Thursday, May 14 EPA RTP campus building C auditorium (Room C111)		
8:30am–8:40	Robert Kavlock	Welcoming Remarks and Goals of the Summit (EPA/ORD/NCCT)
8:40am–9:00	Jim Jones	Using ToxCast™ for Chemical Screening and Prioritization in the Real World (EPA/OPPTS)
9:00am–10:10am		**Introduction to ToxCast– Phase I**
9:00–9:15	David Dix	Overview of the ToxCast™ Research Program: Applications to Predictive Toxicology and Chemical Prioritization (EPA/ORD/NCCT)
9:15–9:45	Keith Houck	Characteristics of the ToxCast™ *In Vitro* Datasets from Biochemical and Cellular Assays (EPA/ORD/NCCT)
9:45–10:00	Matt Martin	Characteristics of the ToxRefDB *In Vivo* Datasets from Chronic, Reproductive and Developmental Assays (EPA/ORD/NCCT)
10:00–10:30		*BREAK--LIGHT REFRESHMENTS PROVIDED*
10:30am–11:30am		**Predicting *In Vivo* Toxicity from ToxCast™ *In Vitro* Data**
10:30–11:00	Richard Judson	onmental Chemicals
11:00–11:30	Barry Hardy	
11:30–12:30		*LUNCH--ON YOUR OWN (there is a café onsite)*
12:30pm–4:45pm		**Mining ToxCast™ Data**
12:30–1:00	Alex Tropsha (U of North Carolina)	Prediction of animal toxicity endpoints of ToxCast Phase I compounds using a combination of chemical and biological *in vitro* descriptors
1:00–1:30	Lyle Burgoon (Michigan State U)	Biomarker Identification using Graph Theoretic and Particle Swarm Optimization-based Support Vector Machine Analysis of the Phase I ToxCast™ Dataset
1:30–2:00	William Welsh (U Med Dentistry NJ)	Biological Spectra Analysis of the Toxcast chemicals: Linkng Bioactivity Profiles to Molecular Structure
2:00–2:30	Rusty Thomas (Hamner Institutes)	An Integrated *In Vitro* and Computational Approach to Define the Exposure-Dose-Toxicity Relationships In High-Throughput Screens
2:30–3:00		*BREAK-- LIGHT REFRESHMENTS PROVIDED*
3:00–3:30	Weida Tong (FDA/NCTR)	Prediction of liver toxicity in the animal study using the mechanistically relevant *in vitro* screening assay data
3:30–4:00	Fred Wright (U North Carolina)	Prediction of *in vivo* toxicity endpoints from ToxCast Phase I data using a variety of machine learning approaches
4:00–4:30	Alison Motsinger (NC State U)	Predictive Modeling of Toxicity Outcomes with Grammatical Evolution Neural Networks
4:30–4:45	Open Discussion on ToxCast™ Predictive Modeling, Introduction to Poster Session	

Data Exploration

2nd ToxCast Data Summit (2014)



Agenda

Data Summit Objectives: To bring together the user community (industry, non-governmental organizations, academia, governmental agencies, and more) to:

- present ideas for using massive amounts of new chemical data, and
- begin a dialogue about how to implement these ideas to inform chemical policy and regulatory decisions.

Day 1 – Monday, September 29, 2014

8:00 am	Registration
8:45 am	Welcome and Overview of Data Summit Objectives Rusty Thomas, Director, U.S. Environmental Protection Agency (EPA) National Center for Computational Toxicology (NCCT)
Regulatory Applications and Data Use	
8:55 am	Keynote ToxCast: From Development to Implementation – A Regulatory Perspective Jim Jones, Assistant Administrator for the Office of Chemical Safety and Pollution Prevention, EPA
9:25 am	Q&A
9:35 am	Assessing the Biological ata from ToxCast Warren Casey, Director teragency Center for the Evaluation of Alternative Toxicological Methods, National Institutes of Environmental Health Sciences
10:00 am	Q&A
10:10 am	Break
10:25 am	An Exposure:Activity Profiling Method for Interpreting High-Throughput Screening Data for Estrogenic Activity—Proof of Concept Rick Becker, Senior Director, American Chemistry Council
10:45 am	Q&A
10:55 am	Evaluating the Potential of ToxCastTM to Inform the Assessment of Existing Substances Under the Chemicals Management Plan: Phthalates As a Case Study Andy Nong, Lead Computational Toxicologist, Health Canada and Tara Barton-Maclaren, Manager, Hazard Methodology, Existing Substances Risk Assessment Bureau, Health Canada
11:20 am	Q&A
11:30 am	Analysis of Pfizer Compounds in EPA's ToxCast Chemicals Assay Space Falgun Shah, Senior Scientist, Pfizer
11:55 am	Q&A
12:05 pm	Lunch on your own (EPA cafeteria) and posters will be available for viewing (Atrium B)

Application

With That Evolution Comes Greater Scrutiny and Higher Expectations

Decision Context is an Important Determinant

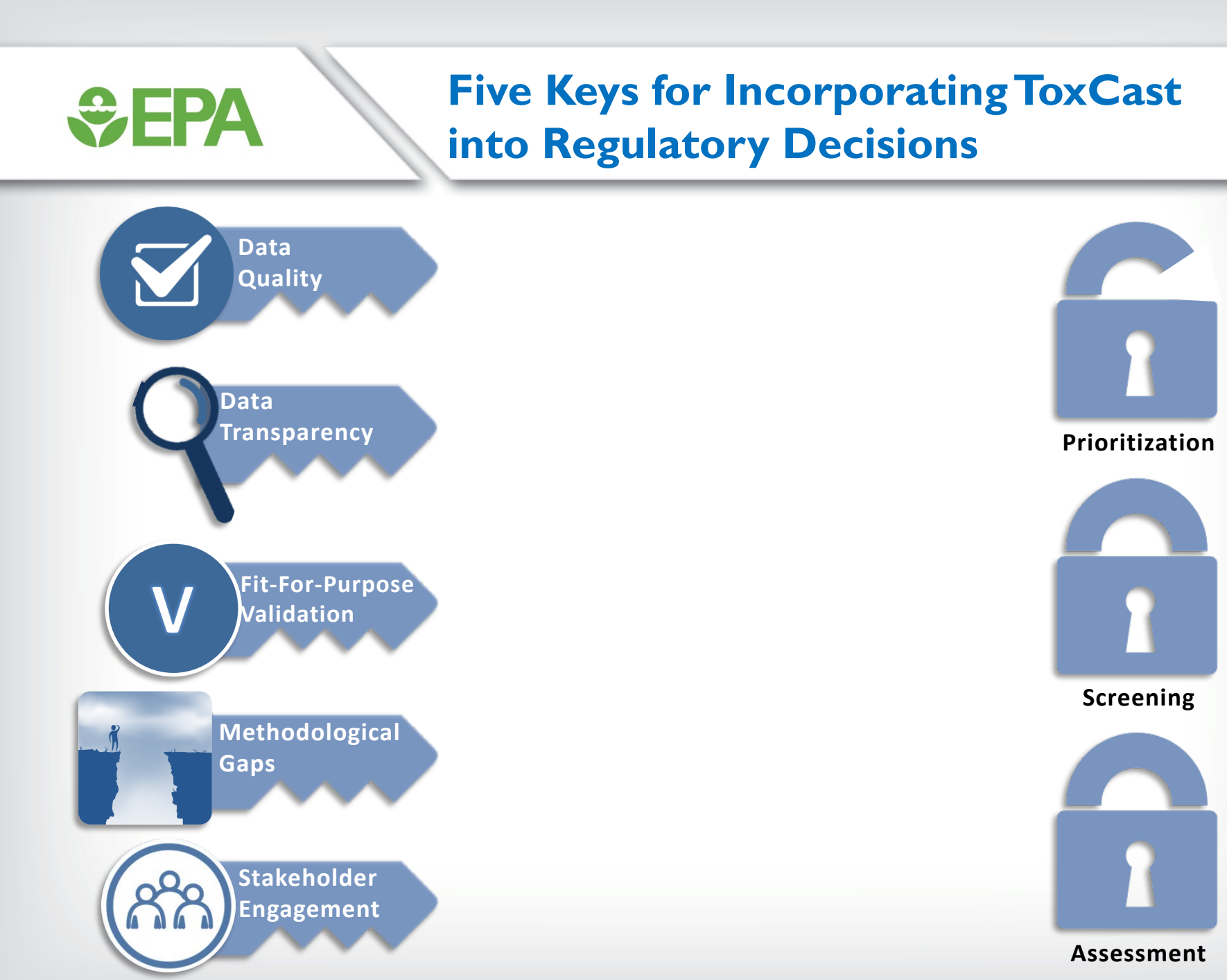
Prioritization

Screening

Assessment

Five Keys for Incorporating ToxCast into Regulatory Decisions

- Data Quality
- Data Transparency
- Fit-For-Purpose Validation
- Methodological Gaps
- Stakeholder Engagement

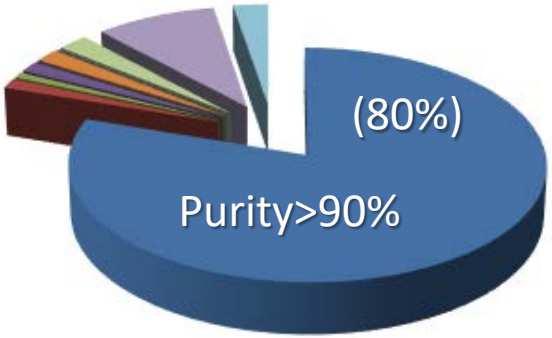


Data Quality

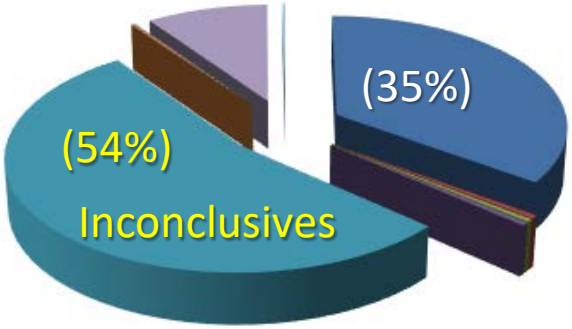
- **Data pipeline revamp and consolidation**
  - More robust and statistically rigorous
  - Data caution flags
  - Release of updated data as zip file (Early October)
  - Updated Dashboard (Late October/Early November)
- **External data audit**
  - Verification of pipeline function and output
  - Evaluation of curve fits
  - Complete in 2015
- **Analytical QC on chemical libraries**
  - LC/MS run complete, follow-up runs on inconclusives ongoing
  - LC/MS runs on stability samples
  - GC/MS runs (Mid October)

Progress on Analytical QC

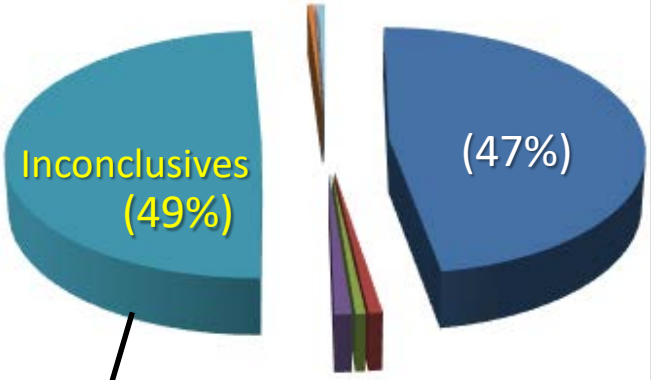
NCGC (NCATS) - Drugs



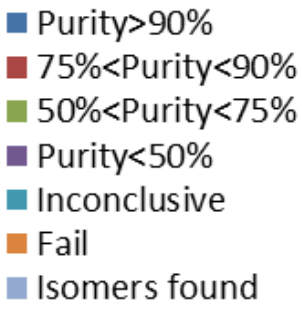
NTP – Industrial/Environ

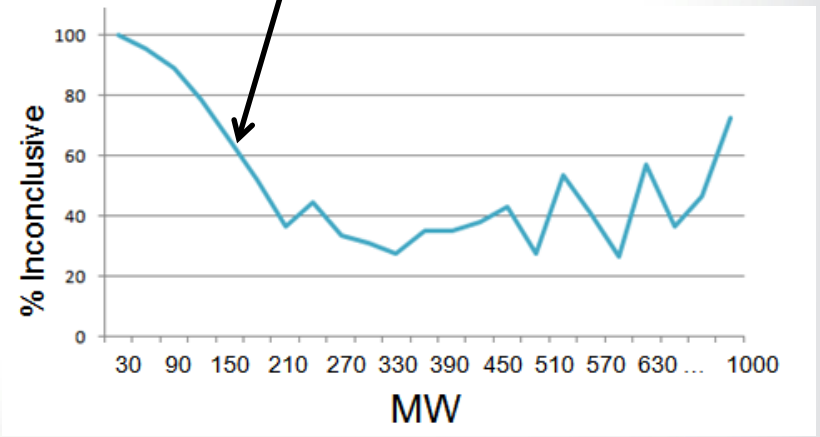


EPA – Industrial/Environ



- "Inconclusives" require additional follow-up & method development
- NTP & EPA libraries contain much higher proportion of inconclusives (e.g., low MW cmpds, dyes, metals)
- Very low "fail" rate





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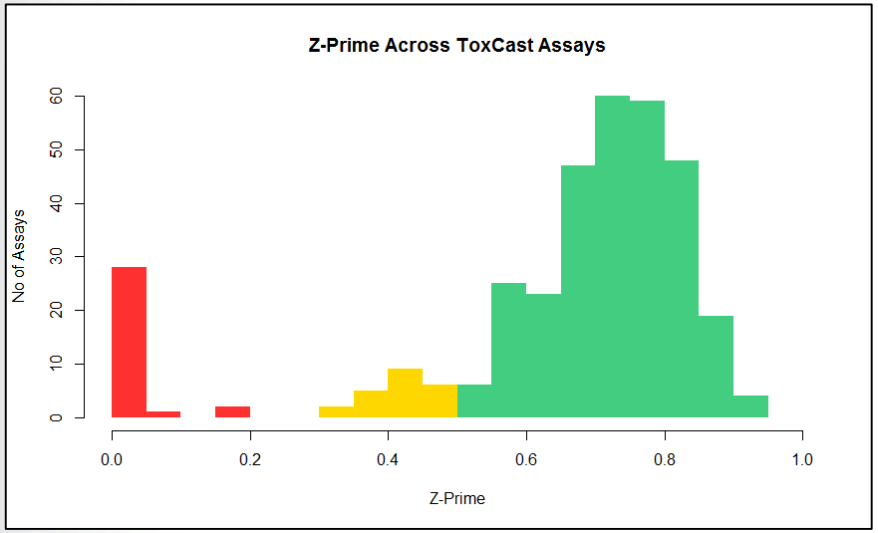
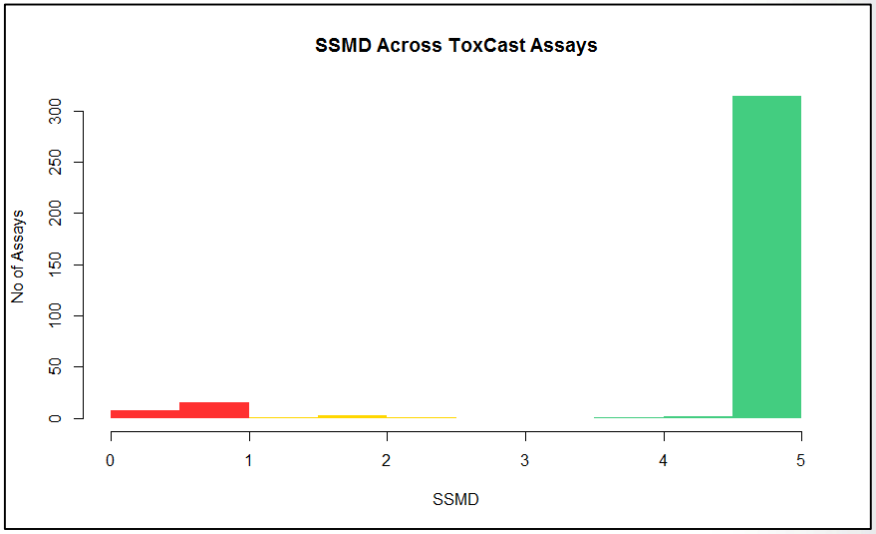
Data Transparency

- Availability of raw and processed data
- Public release of new data pipeline
  - R-package in CRAN (November)
- Development of ToxCast 'Owners Manual'
  - Chemical Procurement and QC
  - Data Analysis
  - Assay Description & Performance Characteristics
  - Planned release in December
- Computational model archive

Assay Performance Characteristics





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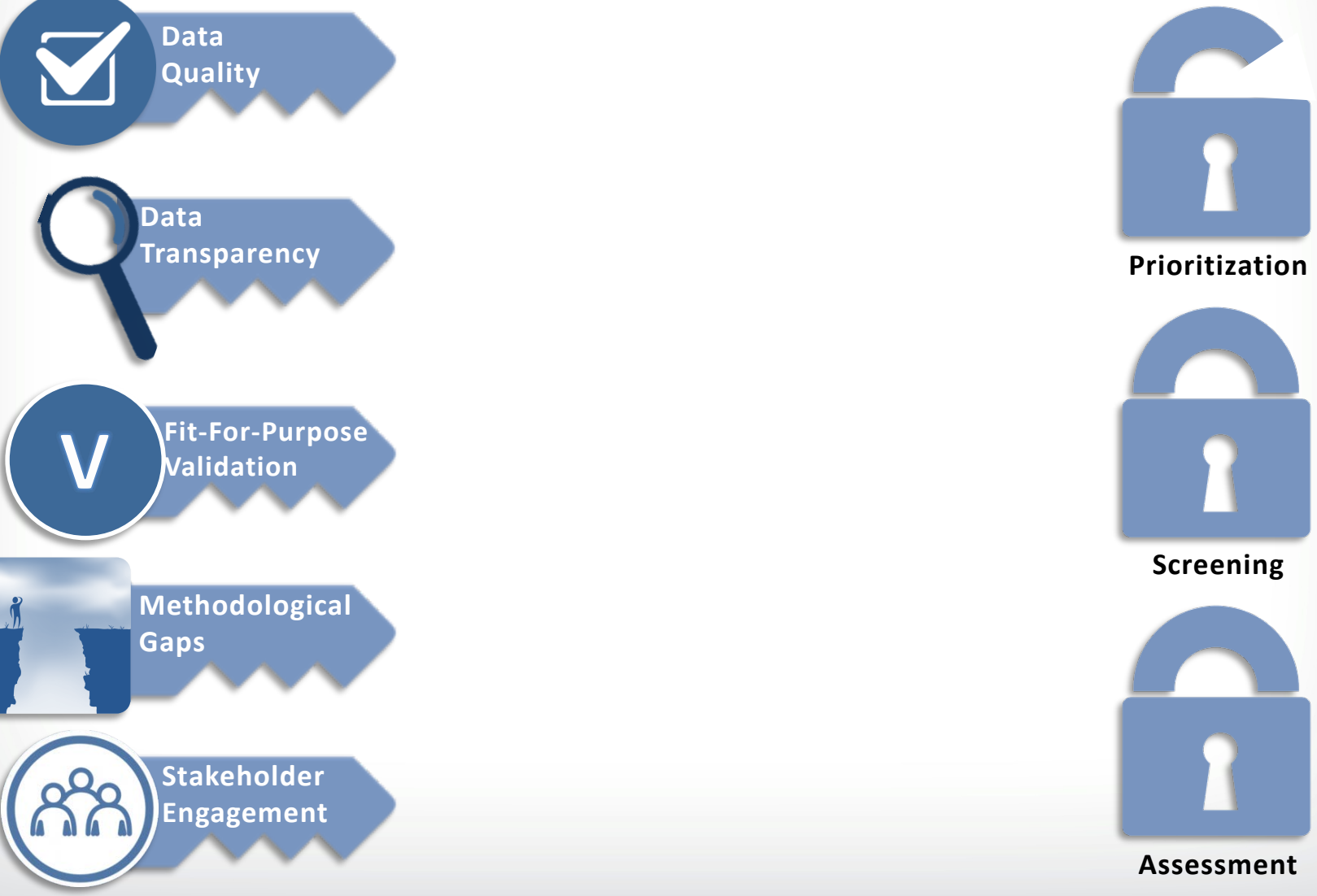

Performance Validation Framework

Perspectives on Validation of High-Throughput Assays Supporting 21st Century Toxicity Testing

Richard Judson[1], Robert Kavlock[1], Matt Martin[1], David Reif[1], Keith Houck[1], Thomas Knudsen[1], Ann Richard[1], Raymond R. Tice[2], Maurice Whelan[3], Menghang Xia[4], Ruili Huang[4], Christopher Austin[4], George Daston[5], Thomas Hartung[6], John R. Fowle III[10], William Wooge[8], Weida Tong[9], and David Dix[1]

ALTEX 30(1):51-6, 2013

- **Follow current validation practice to the extent possible and practical**
- **Make increased use of reference compounds to better demonstrate assay reliability and relevance**
- **Implement a web-based, transparent, and expedited peer review process**

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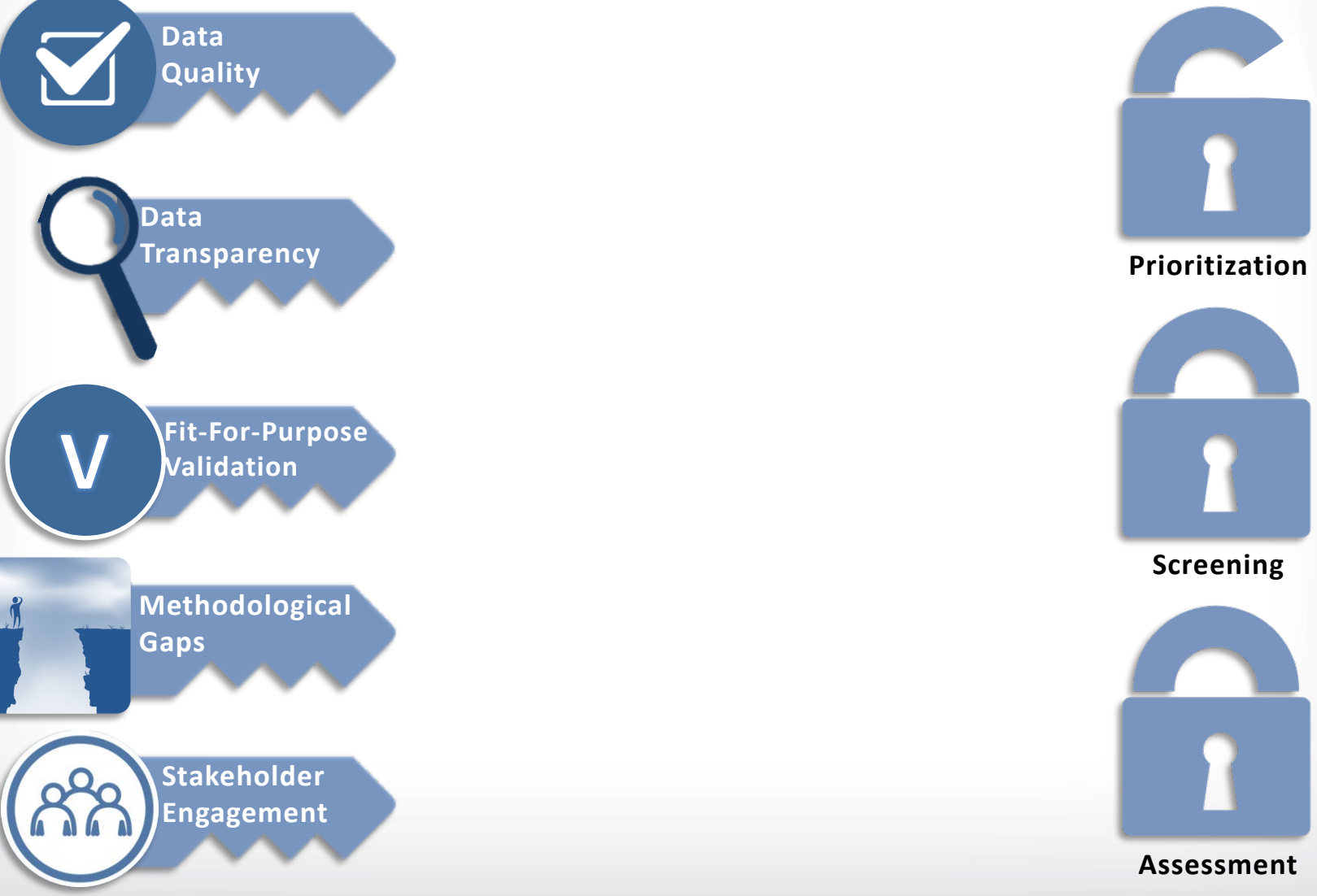

Methodological Gaps

- Metabolic competence of assays
  - Internal research effort
  - Yet2 technology scouting
  - Gated challenge
- Biological space covered by current assays
  - Evaluation of high-throughput transcriptomic assay
- Chemical space covered by library
  - Other vehicles (e.g., water)
  - Volatiles

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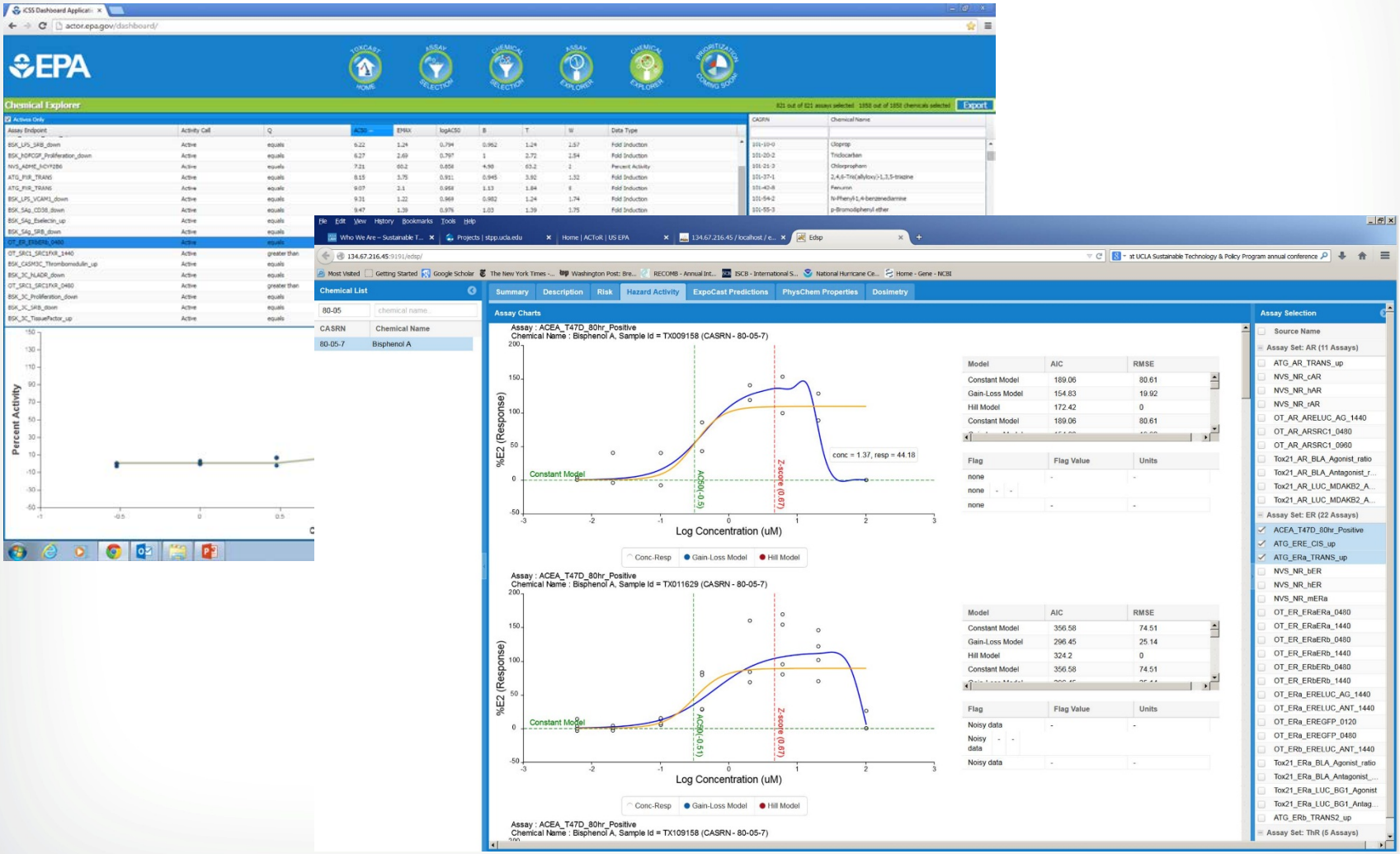
Stakeholder Engagement

- Development of the iCSS Dashboard
  - http://actor.epa.gov/dashboard/
- Release of the iCSS Dashboard Training Videos
  - http://epa.gov/ncct/toxcast/data.html
- ToxCast Stakeholder Workshops and Data Summit
- ToxCast Communities of Practice

Dashboard Development



Thank You from the NCCT Team!